Annals of Clinical and Analytical Medicine
Original Research

Genetic spectrum of familial hypertriglyceridemia from the southeastern region of Turkey

The genetics of familial hypertriglyceridemia

Ayse Ergul Bozaci[1], Aysel Tekmenuray Ünal[2], Fatma Demirbaş[3], İbrahim Taş[1], Mehmet Nuri Ozbek[4]
[1] Department of Pediatric Metabolism, Diyarbakır Children's Hospital
[2] Department of Medical Genetics, Gaziyasargil Research and Training Hospital
[3] Department of Pediatric Gastroenterology and Hepatology, Diyarbakır Children's Hospital
[4] Department of Pediatric Endocrinology, Gaziyasargil Research and Training Hospital, Diyarbakir, Turkey

Abstract

Aim: The disorders of lipid metabolism that cause primary hypertriglyceridemia result from genetic defects in triglyceride synthesis and metabolism. Although primary causes are rare in hypertriglyceridemia, they should be considered in severe hypertriglyceridemia cases. Identified genetic mutations are LPL, APOC2, APOA5, LMF1 and GPIHBP1 mutations.

Material and Methods: This descriptive cross-sectional study was conducted in Diyarbakir Children's Hospital pediatric metabolism clinic on 60 patients from 41 unrelated families who were followed and diagnosed with severe hypertriglyceridemia based on clinical presentation, neurological parameters, biochemical measurements, and molecular analysis. The LPL, APOC2, APOA5, LMF1, GPIHBP1 genes were sequenced in 60 patients. Patients with initial triglyceride levels >885mg/dL were included in the study. Patients with a secondary cause were excluded from the study.

Results: Rare DNA sequence variants were identified in 49 patients (81.66%), including variants LPL (n=15), APOC2 (n=32), and APOA5 (n=2). No mutations were found in 11 patients (21%). The mean initial triglyceride level was 4322.8±4483mg/dL. Acute pancreatitis occurred in 38.33% (n=23) of the patients. The incidence of eruptive xanthoma was 28.33%, organomegaly was 23.33%, and failure to thrive was 21.66%. 69.23% of the patients with failure to thrive were patients with pancreatitis. Two different variants, c.55+6T>G and c.55+1G>C were detected in the APOC2 gene, seven different variants one of which is novel, c.557G>A, c.953A>G, c.296T>C, c.662T>C, c.1262G>A, c.644G>A and c.679G>C, were detected in the LPL gene, and two different variants one of which is novel, c.334_399dup65bp and c.16_39del24bp were detected in the APOA5 gene. Six patients were homozygous for both c.557G>A and c.953A>G variants.

Discussion: The frequency of mutations in APOC2 was 50%, LPL was 25% and APOA5 was %3.33. The relatively high prevalence of APOC2 mutations in our cohort may be due to regional frequency. The development of new therapeutic options for this rare disease requires awareness and screening among these patients. These findings highlight the need for molecular analysis in patients with severe HTG. It is anticipated to guide future individualized therapeutic strategies.

Keywords

Hypertriglyceridemia, Lipoprotein Lipase, APOC2, Acute Pancreatitis

DOI: 10.4328/ACAM.21880 Received: 2023-08-17 Accepted: 2023-09-21 Published Online: 2023-09-23 Printed: 2023-09-25 Ann Clin Anal Med 2023;14(Suppl 2):S180-185
Corresponding Author: Ayse Ergul Bozaci, Department of Pediatric Metabolism, Diyarbakır Children's Hospital, Diyarbakir, Turkey.
E-mail: ergul.acar@yahoo.com.tr P: +90 236 229 26 00
Corresponding Author ORCID ID: https://orcid.org/0000-0002-9783-1016
This study was approved by the Ethics Committee of Diyarbakır Gazi Yaşargil Research and Training Hospital (Date: 2021-12-31, No: 966)

Introduction

Severe hypertriglyceridemia is characterized by plasma triglyceride levels > 885mg/dL (>10.0 mmol/L) in the fasting state (>12 hours) [1]. It is known that the genetic etiology is extremely complex, and both common and rare variants are effective. Moderate elevation of triglyceride (177-885 mg/dL or 2.0-10.0 mmol/L) may be a condition resulting from the polygenic effect of multiple genes and secondary causes [2]. However, it has been determined that mutations in six genes (LPL, APOC2, APOA5, LMF1, GPIHBP1 and GPD1) show severe hypertriglyceridemia (HTG) due to disruption of chylomicron removal pathways. Dietary fats are absorbed from the intestine and transported as triglycerides (TG) in chylomicrons [3]. Chylomicrons that enter the blood begin to degrade when the APOC2 they carry is recognized by lipoprotein lipase (LPL, EC 3.1.1.34). When this process is impaired or insufficient, chylomicron particles accumulate in the plasma and cause hypertriglyceridemia [4]. It has been determined that familial hypertriglyceridemia occurs in the presence of biallelic mutations in the LPL, APOC2, APOA5, LMF1 and GPIHBP1 genes. Clinical features include recurrent pancreatitis, organomegaly, growth retardation, eruptive xanthomas and lipemia retinalis [2]. General circulating persistence of chylomicron is associated with free fatty acid toxicity and, together with its proinflammatory properties, is a trigger for pancreatitis [5]. Pancreatitis due to hypertriglyceridemia is more serious and has a higher complication rate compared to other causes [4]. Lipoprotein electrophoresis was not performed due to technical incompetence. Also, Fredrickson's classification is not useful in daily practice.

In patients with severe HTG, omega-3, medium chain triglyceride (MCT) and fenofibrates are used in the treatment [6]. However, since therapeutic interventions to reduce TG levels are often ineffective, individualized therapeutic strategies targeting its molecular basis are being developed. Therefore, we aim to evaluate the coexistence of severe HTG and pancreatitis and to define the variants that cause monogenic HTG in our center.

Material and Methods

Study design and data acquisition

This descriptive cross-sectional study was conducted at Diyarbakır Children's Hospital pediatric metabolism clinic on 60 patients from 41 unrelated families who were followed and diagnosed with severe hypertriglyceridemia based on clinical presentation, neurological parameters, biochemical measurements, and molecular analysis. Patients with initial triglyceride levels >885 mg/dL were included in the study. Patients with body weight <-2 SDS under 2 years of age, and patients with body mass index <-2 SDS over 2 years of age were considered as failure to thrive. Patients with a secondary cause were excluded from the study. Inclusion criteria were rare biallelic variants in LPL, APOC2, APOA5, LMF1, GPIHBP1 genes classified as likely pathogenic or pathogenic according to the American College of Medical Genetics and Genomics/ Association for Molecular Pathology guidelines.

Molecular Analyses

All exons and exon-intron junctions of the genes were evaluated by the next-generation sequencing method. Genomic DNA was extracted from peripheral blood samples using a QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. Standardized PCR pools were prepared using NexteraXT sample preparation kit for next-generation sequencing analysis with the Miseq device (Illumina, Inc.). Sanger sequencing of genomic variants identified by exome sequencing or targeted gene sequencing was performed for all patients and their families. Sanger sequencing was used to validate pathogenic variants within families on 3500 genetic analyzer (Applied Biosystems, Foster City, USA). The sequencing results were analyzed using CLC genomic workbench software. For clinical interpretation of variants, allele frequency data were obtained from various databases, including gnomAD (http://gnomad.broadinstitute.org/) and ExAc (http://exac.broadinstitute.org/). The pathogenicity of variants was assessed using in silico prediction tools, such as PolyPhen-2 (http://genetics.bwh. harvard.edu/pph2), SIFT (http://sift.jcvi.org), and MutationTaster (http: // www. mutationtaster.org) and Human Splicing Foundation (http://www.umd.be/hsf/).

Ethical Approval

The study involving the use of human subjects was conducted in accordance with all the relevant national regulations, institutional policies and in accordance with the tenets of the Helsinki Declaration and has been approved by the the local Diyarbakır Gaziyaşargil Research and Training Hospital Ethics Committee (Date: 31-12-2021/No966).

Statistics

Statistical analyses of the data were performed using the SPSS software package for Windows software package (ver.18.0; SPSS Inc., Chicago, IL, USA). As descriptive statistics, numbers, and percentages for categorical variables, mean±standard deviation or median (minimum-maximum) were used for numerical variables. The distribution of data was evaluated using the Shapiro-Wilk test. For numerical comparisons, Student's t-test or Mann-Whitney U- test was used to assess differences between two groups according to the normal distribution of the measured parameters.

Results

A total of 60 patients, 26 female and 34 male, from 45 different families were included in the study. None of the patients have been previously published. The consanguinity rate was 96.66%. The mean age at the time of the data collection was 5.31±4.37 years (min: 6 months max: 14 years). The mean age at diagnosis was 2.62±3.90 years (min: 7 days max: 13 years). The total duration of follow-up of the cohort was three years, individually ranging from 4 to 46 (median = 12.1) months.

Rare DNA sequence variants were identified in 49 patients (81.66%), including variants LPL (n=15), APOC2 (n=32), APOA5 (n=2). No mutation was detected in 11 patients (21%). The mean age at diagnosis of APOC2 patients was 2.95±4.18 years, LPL patients was 2.97±4.33 years. There was no significant difference between the mean age at diagnosis between genetic defects. 15/23 patients had recurrent pancreatitis. Initial TG levels in patients with APOC2 were significantly higher than in those with LPL ($p<0.05$). The clinical and laboratory characteristics according to the gene defects are shown in Table 1.

Table 1. Clinical and laboratory characteristics according to the genetic defects.

Patient groups	Mean Initial Triglyceride Levels mg/dL (n,%)	Mean Undertreatment, Triglyceride Levels mg/dL (n,%)	Acute Pancreatitis (n,%)	Mean Number of Pancreatic Episodes	Organomegaly	Eruptive Xanthoma
APOC2 patients (n=32)	4736.9±5320.6 (min:945, max:20.898)	1035.31±564.65 (min:420 max:2400)	11 (34.37%)	2.07±0.99	9 (29.12%)	9 (29.12%)
LPL patients (n=15)	2764.2±1901.5 (min:914 max:6681)	1469.06±1151.55 (min:281 max:4200)	6 (40%)	2.83±1.57	4 (26.66%)	4 (26.66%)
Mutation not found (n=11)	4720.2±3959 (min:985 max:12980)	2217.72±1929.97 (min:435 max:6670)	4 (36.36%)	1.5±0.5	0	3 (27.27%)
Total (n=60)	4322.8±4483.6 (min:914 max:20898)	1417.81±1232.72 (min:281 max:6670)	23 (38.33%)	2.31±1.25	13 (23.33%)	17 (28.33%)

Table 2. Clinical and laboratory characteristics of patients with pancreatitis and patients without pancreatitis.

	Patients with Pancreatitis Episodes (n=23)	Patients without Pancreatitis Episodes (n=37)
APOC2 (n, %)	11 (47.82%)	21 (56.75%)
LPL (%)	6 (26%)	5 (24.32%)
Mean Initial Triglyceride level (mg/dL)	4890.72±4689.51	3943.63±4437.76
Failure to Thrive (%)	9 (39.13%)	4 (10.81%)
Organomegaly (%)	5 (21.13%)	6 (16.21%)

The mean age of the patients with pancreatitis in patients with pancreatitis was 2.62±3.81 years, and of patients without pancreatitis it was 2.73±4.03 years. Triglyceride levels of the patients with pancreatitis at the time of diagnosis were found significantly higher ($p<0.05$). Failure to thrive was observed more frequently in patients with pancreatitis. The clinical and laboratory characteristics of patients with pancreatitis and without pancreatitis are presented in Table 2.

Dietary treatment was applied in all patients. The recommended fat intake for patients was 10–15% of their total caloric intake. MCT oil was recommended to be 50-80% of total fat. Low-fat, medium chain triglyceride (MCT) oil-rich formula was used in infants under 1 year old. Lipid restriction and MCT oil supplementation were performed in patients older than 1 year. Omega 3 was given to 54 patients older than three months old. Fenofibrate was received by six patients. When the mean undertreatment TG levels were evaluated, no significant difference was found between the groups.

A total of 47 pancreatitis episodes were recorded. Therapeutic apheresis was performed in six patients due to severe pancreatic episodes. Three sessions of TA were performed in 2/6 patients, and one session in 4/6 patients. Triglyceride levels were measured after each TA and continued until <1000 mg/dL. Necrotizing pancreatitis was observed in two patients. In the follow-up, pancreatic enzyme supplementation was started due to exocrine pancreatic insufficiency.

Two different variants, c.55+6T>G and c.55+1G>C were detected in the APOC2 gene. A c.55+6T>G (IVS2+6T>G) intronic variant was detected in 22 patients from 11 families. This variant has so far been considered a “variant of uncertain significance (VUS)” because it is extremely rare (PM2) in healthy population databases and deleterious (PP3) in in-silico prediction tools. The c.55+1G>C (IVS2+1G>C) splice-site variant was detected in the APOC2 gene in 10 patients. Seven different variants, c.557G>A, c.953A>G, c.296T>C, c.662T>C, c.1262G>A, c.644G>A and c.679G>C were detected in the LPL gene. Both c.557G>A p.Gly186Glu (G186E) and c.953A>G p.Asn318Ser (N318S) (double homozygous variants) variants in the LPL gene were homozygous in six patients. In the F30, c.644G>A p.Gly215Glu(G215E) heterozygous and c.679G>C p.Val227Leu(V227L) heterozygous variants were found as compound in two siblings. c.679G>C p.Val227Leu variant is novel. In P48, the c.334_399dup p.Ala112_Thr133dup variant was homozygous in the APOA5 gene. This variant is a novel variant. Molecular analysis results are shown in Table 3.

Discussion

Familial hypertriglyceridemia is a rare cause of severe triglyceride elevation, which is seen with a prevalence of 1 in 1.000.000 [2]. The LPL, APOC2, APOA5, LMF1, GPIHBP1 genes have been identified as the causative genes of monogenic chylomicronemia [7]. These genes are necessary for the normal functioning of the LPL enzyme. Loss-of-function mutations in the LPL pathway could be detected in less than 30-40% of familial HTG patients [8,9]. In patients without genetic mutation, the underlying cause may be the development of autoantibodies against proteins in the LPL pathway or additional genetic factors. In our study group, LPL, APOC2, APOA5, LMF1 and GPIHBP1 genes were analyzed in 60 patients. A total of 11 different variants were detected in 81.66% (n=49) of patients, including two novel variants. The reason why this rate is higher than in other studies may be due to very high consanguinity rates (96.66%) or very strict inclusion criteria.

In familial HTG, the LPL gene was the most commonly affected gene in the literature [8-10]. The most commonly affected gene was APOC2 in our study group and the prevalence of APOC2 variants was high compared to previous observations [8,9]. The c.55+6T>G (IVS2+6T>G) intronic variant was detected in 22 patients in our study. This variant has so far been considered a “variant of unsignificant (VUS)” because it is extremely rare (PM2) in healthy population databases and deleterious (PP3) in in-silico prediction tools. This mutation was detected in a Turkish infant and three Turkish adult patients with hypertriglyceridemia [11,12]. Since it was detected in 22 familial HTG cases in our study, it was thought that it would be appropriate to classify it as a “likely pathogenic/pathogenic”. Additionally, the higher proportion of cases with this variant in our Turkish cohorts could reflect ascertainment bias or possible founder effect of this variant.

In our study, the LPL gene was the second most affected gene. The c.557G>A p.Gly186Glu (G186E) and c.953A>G p.Asn318Ser

Table 3. Molecular characteristics of familial hypertriglyceridemia patients.

Family	Patient Number	Gene	Molecular analyses	Pathogenicity
F1	P1	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F1	P2	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F1	P3	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F1	P4	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F1	P5	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F1	P6	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F2	P7	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F2	P8	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F2	P9	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F3	P10	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F3	P11	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F4	P12	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F4	P13	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F5	P14	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F5	P15	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F6	P16	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F6	P17	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F7	P18	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F8	P19	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F9	P20	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F10	P21	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F11	P22	APOC2	c.55+6T>G IVS2+6T>G homozygous	Likely pathogenic
F12	P23	APOC2	c.55+1G>C IVS2+1G>C homozygous	Pathogenic
F12	P24	APOC2	c.55+1G>C IVS2+1G>C homozygous	Pathogenic
F13	P25	APOC2	c.55+1G>C IVS2+1G>C homozygous	Pathogenic
F13	P26	APOC2	c.55+1G>C IVS2+1G>C homozygous	Pathogenic
F14	P27	APOC2	c.55+1G>C IVS2+1G>C homozygous	Pathogenic
F15	P28	APOC2	c.55+1G>C IVS2+1G>C homozygous	Pathogenic
F16	P29	APOC2	c.55+1G>C IVS2+1G>C homozygous	Pathogenic
F17	P30	APOC2	c.55+1G>C IVS2+1G>C homozygous	Pathogenic
F18	P31	APOC2	c.55+1G>C IVS2+1G>C homozygous	Pathogenic
F19	P32	APOC2	c.55+1G>C IVS2+1G>C homozygous	Pathogenic
F20	P33	LPL	c.557G>A p.Gly186Glu (G186E) homozygous/ c.953A>G p.Asn318Ser (N318S) homozygous	Pathogenic/VUS
F20	P34	LPL	c.557G>A p.Gly186Glu (G186E) homozygous/ c.953A>G p.Asn318Ser (N318S) homozygous	Pathogenic/VUS
F20	P35	LPL	c.557G>A p.Gly186Glu (G186E) homozygous/ c.953A>G p.Asn318Ser (N318S) homozygous	Pathogenic/VUS
F21	P36	LPL	c.557G>A p.Gly186Glu (G186E) homozygous/ c.953A>G p.Asn318Ser (N318S) homozygous	Pathogenic/VUS
F22	P37	LPL	c.557G>A p.Gly186Glu (G186E) homozygous/ c.953A>G p.Asn318Ser (N318S) homozygous	Pathogenic/VUS
F23	P38	LPL	c.557G>A p.Gly186Glu (G186E) homozygous/ c.953A>G p.Asn318Ser (N318S) homozygous	Pathogenic/VUS
F24	P39	LPL	c.296T>C p.Leu99Pro (L99P) homozygous	Pathogenic
F24	P40	LPL	c.296T>C p.Leu99Pro (L99P) homozygous	Pathogenic
F25	P41	LPL	c.296T>C p.Leu99Pro (L99P) homozygous	Pathogenic
F26	P42	LPL	c.662T>C p.Ile221Thr (I221T) homozygous	Pathogenic
F27	P43	LPL	c.662T>C p.Ile221Thr (I221T) homozygous	Pathogenic
F28	P44	LPL	c.662T>C p.Ile221Thr (I221T) homozygous	Pathogenic
F29	P45	LPL	c.1262G>A p.Trp421Ter (W421*) homozygous	Pathogenic
F30	P46	LPL	c.644G>A p.Gly215Glu(G215E) heterozygous/ c.679G>C p.Val227Leu(V227L) heterozygous	Pathogenic/ Likely pathogenic
F30	P47	LPL	c.644G>A p.Gly215Glu(G215E) heterozygous/ c.679G>C p.Val227Leu(V227L) heterozygous	Pathogenic/ Likely pathogenic
F31	P48	APOA5	c.334_399dup p.Ala112_Thr133dup homozygous	Likely pathogenic
F32	P50	APOA5	c.16_39del24bp homozygous	Pathogenic

Novel mutations are shown in bold.

(N318S) variants were found double homozygous in the LPL gene in six patients. The c.557G>A p.Gly186Glu variant is a pathogenic variant that has been previously reported [13]. The c.953A>G p.Asn318Ser variant has been reported in the ClinVar database with different classifications as pathogenic, VUS, and benign. Although, this variant was evaluated as a polymorphism but associated with increased cardiovascular risk. In addition, this variant has also been shown to reduce LPL activity [14,15]. The c.953A>G p.Asn318Ser variant, which was detected as a double homozygous mutation in six patients, the clinical

significance of this variant cannot be commented on since the c.557G>A p.Gly186Glu variant is pathogenic. The c.644G>A variant was previously reported as pathogenic [15,16]. The c.1262G>A p.Trp421Ter (W421*), c.644G>A p.Gly215Glu (G215E) variants in the LPL gene has also been reported previously and are classified as pathogenic [13]. The c.679G>C p.Val227Leu variant is novel. The amino acid valine at position 227 is a conserved amino acid in protein; previously reported as c.679G>T p.Val227Phe (V227F) in a patient as a pathogenic in the form of different amino acid conversion with different nucleotide change. In another patient, it was reported as likely pathogenic as c.680T>C p.Val227Ala conversion to a different aminoacids (ClinVar#2441229). The c.334_399dup p.Ala112_Thr133dup variant in APOA5 gene is novel variant. This variant was classified as likely pathogenic because the patient had hypertriglyceridemia, although it was evaluated as VUS in databases such as Varsome and Franklin, but not found in healthy population databases. The c.16_39del p.Ala6_Ala13del (A6_A13del) variant in the APOA5 gene was previously reported. Initial TG levels of patients with APOC2 gene defect were significantly higher than those with LPL gene defect ($p<0.05$). The significant difference in mean initial triglyceride levels of the APOC2 and LPL genes may be due to the different sample size and small number of subgroups.

Severe HTG is an independent risk factor for pancreatitis. TG level ≥1000 mg/dL is usually indicated as the threshold for the development of pancreatitis [17]. However, some studies argue that TG>500mg/dL increases the risk of pancreatitis [6]. Acute pancreatitis was observed in 38.33% of the patients, and recurrent pancreatitis was observed in 65.21% of them. Triglyceride levels of the patients with pancreatitis at the time of diagnosis were found significantly higher than the without pancreatitis patients ($p<0.05$). Consistent with the literature, the frequency of pancreatitis was higher in patients with higher triglyceride levels in our study. To prevent pancreatitis, therapeutic plasmapheresis has been included in the guidelines as an option [18-20]. We also performed TA in six patients because of severe pancreatitis unresponsive to medical treatment and poor general condition. In our study, triglyceride levels were measured after each TA and continued until <1000 mg/dL. In most of our patients, triglyceride levels decreased after one session.

MCT-rich low-fat diet, fenofibrates are not effective enough to reduce TG levels in patients with severe HTG [21]. Recently, LPL gene therapy (Alipogene tiparvovec), APOC3 inhibitors (Volanesorsen), ANGPTL3 and ANGPTL4 inhibitors have been developed and evaluated in clinical trials [22]. The development of new therapeutic options for this rare disease requires awareness and screening among these patients. These findings highlight the need for molecular analysis in patients with severe HTG. It is anticipated to guide future individualized therapeutic strategies.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Funding: *None*

Conflict of interest

The authors declare no conflict of interest.

References

1. Krasi G, Bushati V, Precone V, Cortese B, Agostini F, Tezzele S, et al. Monogenic hyperlipidemias. Acta Biomed. 2019;90(10-S):47-9.

2. Goldberg RB, Chait A. A comprehensive update on the chylomicronemia syndrome. Front Endocrinol. 2020;11:593931.

3. Brunzell JD, Deeb SS. Familial lipoprotein lipase deficiency, apoC-II deficiency, and hepatic lipase deficiency. The metabolic and molecular bases of inherited disease. 2001; 2:2789-816.

4. Burnett JR, Hooper AJ, Hegele RA. Familial Lipoprotein Lipase Deficiency [Internet]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJ, Stephens K, Amemiya A, editors. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993.

5. Xu T, Sheng L, Guo X, Ding Z. Free Fatty Acid Increases the Expression of NLRP3-Caspase1 in Adipose Tissue Macrophages in Obese Severe Acute Pancreatitis. Dig Dis Sci. 2022;67(6):2220-31.

6. Subramanian S. Approach to the Patient with Moderate Hypertriglyceridemia. J Clin Endocrinol Metab. 2022;107(6):1686-97.

7. Brahm AJ, Hegele RA. Chylomicronaemia-current diagnosis and future therapies. Nat Rev Endocrinol. 2015; 11(6): 352-62.

8. Surendran RP, Visser ME, Heemelaar S, Wang J, Peter J, Defesche JC, et al. Mutations in LPL, APOC2, APOA5, GPIHBP1 and LMF1 in patients with severe hypertriglyceridaemia. J Intern Med. 2012; 272(2):185-96.

9. Rabacchi C, Pisciotta L, Cefalù AB, Noto D, Fresa R, Tarugi P, et al. Spectrum of mutations of the LPL gene identified in Italy in patients with severe hypertriglyceridemia. Atherosclerosis. 2015; 241(1):79-86.

10. Soyaltın UE, Bozkurt ABK, Solmaz, AE, Hakverdi G, Sımsır IY. Prevalence of lipoprotein lipase mutation in patients with severe hypertriglyceridemia and the characteristic features of hypertriglyceridemic pancreatitis. Ege Journal of Medicine. 2022:61(4): 658-65.

11. Kose E, Armagan C, Teke Kısa P, Onay H, Arslan N. Severe hyperchylomicronemia in two infants with novel APOC2 gene mutation. J Pediatr Endocrinol Metab. 2018;31(11):1289-93.

12. Abedi AH, Yıldırım Şimşir I, Bayram F, Onay H, Özgür S, Mcintyre AD, et al. Genetic Variants Associated with Severe Hypertriglyceridemia: LPL, APOC2, APOA5, GPIHBP1, LMF1, and APOE. Turk Kardiyol Dern Ars. 2023; 51(1):10-21.

13. Rodrigues R, Artieda M, Tejedor D, Martínez A, Konstantinova P, Petry H, et al. Pathogenic classification of LPL gene variants reported to be associated with LPL deficiency. J Clin Lipidol. 2016;10(2):394-409.

14. López-Ruiz A, Jarabo MM, Martínez-Triguero ML, Morales-Suárez-Varela M, Solá E, Bañuls C, et al. Small and dense LDL in familial combined hyperlipidemia and N291S polymorphism of the lipoprotein lipase gene. Lipids Health Dis. 2009;8:12.

15. Sagoo GS, Tatt I, Salanti G, Butterworth AS, Sarwar N, van Maarle M, et al. Seven lipoprotein lipase gene polymorphisms, lipid fractions, and coronary disease: a HuGE association review and meta-analysis. Am J Epidemiol. 2008;168(11):1233-46.

16. Ashraf AP, Hurst ACE, Garg A. Extreme hypertriglyceridemia, pseudohyponatremia, and pseudoacidosis in a neonate with lipoprotein lipase deficiency due to segmental uniparental disomy. J Clin Lipidol. 2017;11(3):757-62.

17. Valdivielso P, Ramírez-Bueno A, Ewald N. Current knowledge of hypertriglyceridemic pancreatitis. Eur J Intern Med 2014;25(8):689-94.

18. Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011;123(20):2292-333.

19. Connelly-Smith L, Dunbar NM. The 2019 guidelines from the American Society for Apheresis: what's new? Curr Opin Hematol. 2019;26(6):461-5.

20. Kadikoylu G, Yavasoglu I, Bolaman Z. Plasma exchange in severe hypertriglyceridemia a clinical study. Transfus Apher Sci. 2006; 34(3):253-7.

21. Gotoda T, Shirai K, Ohta T, Kobayashi J, Yokoyama S, Oikawa S, et al. Research Committee for Primary Hyperlipidemia, Research on Measures against Intractable Diseases by the Ministry of Health, Labour and Welfare in Japan. Diagnosis and management of type I and type V hyperlipoproteinemia. J Atheroscler Thromb. 2012; 19:1-12.

22. Okazaki H, Gotoda T, Ogura M, Ishibashi S, Inagaki K, Daida H, et al. Current Diagnosis and Management of Primary Chylomicronemia. J Atheroscler Thromb. 2021;28(9):883-904.

How to cite this article:
Ayse Ergul Bozaci, Aysel Tekmenuray Ünal, Fatma Demirbaş, İbrahim Taş, Mehmet Nuri Ozbek*. Genetic spectrum of familial hypertriglyceridemia from the southeastern region of Turkey. Ann Clin Anal Med 2023;14(Suppl 2):S180-185*

This study was approved by the Ethics Committee of Diyarbakır Gazi Yaşargil Research and Training Hospital (Date: 2021-12-31, No: 966)